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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,473	03/01/2002	Melissa K. Carpenter	090/003C	1663

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EXAMINER
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TON, THAIAN N

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 07/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/087,473

Applicant(s)

CARPENTER ET AL.

Examiner

Thaia N. Ton

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 10 May 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,4-6,31 and 32 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,4-6,31 and 32 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

Applicants' Amendment and Remarks, filed 5/10/06, have been entered and considered. Claims 2, 3, 7-30 are cancelled; claim 1 is amended; claims 1, 4-6, 31 and 32 are pending and under current examination.

### *Double Patenting*

The prior provisional rejection of claims 1, 4-6, 30-32 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-46 of copending Application No. 09/888,309 rendered moot in view of abandonment of the '309 application.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-6, 31, 32 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of producing a population of cells that comprise neurons that express tyrosine hydroxylase by plating and culturing undifferentiated human ES cells on a solid surface so that they differentiate without forming embryoid bodies, culturing the plated cells in a medium that contains *noggin* and *follistatin*, harvesting a population of cells from the solid surface, wherein the cells comprise neurons that express tyrosine hydroxylase, does not reasonably provide enablement for the breadth of the claims, utilizing either *noggin* or *follistatin* alone in order to produce neurons that express TH. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' Arguments. Applicants' traverse the basis for the prior rejection, but have amended the claims to specifically recite using noggin and/or follistatin in order to produce a population of cells comprising neurons that expression tyrosine hydroxylase. See page 3 of the Response.

Response to Arguments. These arguments are fully considered, but are not persuasive. The claims recite that the medium can contain noggin and/or follistatin. However, neither the specification, nor any evidence of record provides evidence that using either noggin or follistatin by themselves, would result in the population of cells comprising neurons that expression TH. The prior Office actions have provided evidence that directing differentiation of hES cells is unpredictable (see, for example, Du *et al.*, cited in the Office action mailed 12/17/04), who clearly show that directing differentiation of ES cells to neural cells is inefficient, and that usually this neural differentiation requires aggregation of the cells. The working examples in the specification only provide guidance with regard to noggin and follistatin (Group 5). See Table 3. Table 4 provides the results from these experiments, and it is noted that only those treatments that contain Test Group 5 (*i.e.*, noggin and follistatin in combination) are able to produce any cells with TH positive staining. See Treatments B, D, and F. There is no teaching, guidance or evidence of record to show that utilizing noggin or follistatin by themselves would result in the production TH positive neurons, as required by the claims.

Accordingly, in view of the state of the art with regard to the unpredictable state of the art of directed differentiation of hES cells, and the working examples in the specification, which only provide guidance for using noggin and follistatin to produce neurons, it would have required undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1, 4-6, 31, 32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson *et al.* (*Science*, 282:1145-1147 (1998), Document BC of Applicants' IDS, filed 4/26/02) in view of Weiss and in further view of Melton *et al.* (Weiss and Melton cited in the Office action mailed 5/4/04)

Applicants' Arguments. Applicants' argue that the prior rejection has not presented reasonable and supported arguments that one skilled in the art would

have been motivated to combine the teachings to arrive at the claimed invention. Applicants argue that the Melton reference involve *in vivo* experiments in a frog model, and that these experiments are not involved in any way with ES cells. Further, that why one of skill in the art would expect that using the teachings of Melton, would have reasonably expected noggin and/or follistatin to promote the *in vitro* differentiation of hES cells to neurons that express TH. Furthermore, Applicants argue that there is no specific guidance in Melton with regard to using follistatin in order to produce TH-expressing neurons. Applicants argue that the combination of the three references fail to provide sufficient motivation to arrive at the claimed invention. Applicants argue that because the three references have different starting points (hES cells versus *in vivo* frog versus neural stem cells), and that the Office has not supported the motivation for one of skill in the art to combine the three references to arrive at the claimed invention. Applicants argue that the Office has not explained why the motivation provided in the prior rejection has any relevance with regard to combining the three references to arrive at the claimed invention. Therefore, Applicants conclude that the three references do not render the claimed invention obvious.

Response to Arguments. These arguments are considered, but not persuasive. Thomson *et al.* is provided with regard to human ES cells, and their capability to produce various neural tissues. Although they do not specifically teach plating the cultured cells on a solid surface, and then plating them in a medium that contains noggin and follistatin, and then harvesting a population of TH positive neurons, Weiss and Melton provide sufficient motivation and guidance to do so. Particularly, to address Applicants' arguments that Melton do not teach TH-expressing neurons, the Examiner responds that the claims require a medium containing noggin and/or follistatin. Thus, the medium in step (b) of claim 1 encompasses media that contain noggin and/or follistatin, but can also include other factors, including, for example, neurotrophins, such as NT-3, or BDNF. Weiss teach

that using BDNF and NT-3, TH positive neurons can be produced, see col. 56, Table 1. Furthermore, with regard to Melton, they teach using noggin and/or follistatin to induce neuronal cell differentiation from stem cells. Although, as noted by Applicants', Melton's working examples are primarily directed to frog work (both *in vitro* and *in vivo*), they clearly contemplate using these methods in order to produce human neural cells, for example, in the context of treatment of various diseases, such as Parkinson's disease or Alzheimer's disease (col. 5, lines 38-50). Thus, Melton clearly teaches using their methods for human cells. Furthermore, with regard to using noggin and follistatin, the Examiner provides Smith (**Trends in Genetics**, 15(1): 3-5 (1999), to show that both noggin and follistatin are highly conserved proteins in vertebrates (including frogs and mice). For example, noggin knockout mice begin to show numerous defects, including those of the neural tube, somite and limb (see p. 4, 2<sup>nd</sup> col.). Thus, this provides guidance to show that because these proteins are highly conserved in neural development, one of skill in the art, at the time of filing, would have had the motivation and a reasonable expectation of success to use these factors to culture hES cells to produce neural cells. It is maintained that the combination of Thomson, Melton and Weiss provide sufficient motivation and a reasonable expectation of success to arrive at the claimed invention.

Thomson *et al.* teach the generation of human ES cells from human blastocysts. They teach that the ES cells can generate cells from all three germ layers, including neural tissue and ganglia (see Abstract and page 1146, col. 1, 2<sup>nd</sup> full ¶). Thomson does not teach the replating of the cells on a solid surface that is coated with a polycation, and harvesting the differentiated cells from the solid surface, or culturing the ES cells in a medium that contains a TGF- $\beta$  superfamily antagonist, or culturing the cells in a medium that contains a specific neurotrophin (such as BDNF or NT-3)

However, prior to the time the claimed invention was made, Weiss teach the *in vitro* proliferation and differentiation of neural stem cells. They teach that stem cells give rise to progenitor cells which give rise to proliferating cells, such as neuroblasts, glioblasts, etc. See col. 1, lines 63-67. They teach methods for the *in vitro* differentiation of neural stem cells and stem cell progeny by isolating stem cells from a mammal, exposing the cell to a medium containing a growth factor to induce the cell to proliferate and differentiate. They teach that in the presence of proliferation-inducing growth factor(s), the stem cell divides and gives rise to a sphere of undifferentiated cells, wherein when the cells are dissociated and plated as single cells on a non-adhesive substrate and under conditions that allow differentiation, the cells differentiation into neurons, astrocytes and oligodendrocytes. See col. 11, lines 39-50. In particular, the dissociated neural cells can be induced to differentiate by culturing the cells on a substrate such as poly-ornithine treated glass or plastic to differentiate into neurons and glial cells. See col. 18, lines 30-55. Furthermore, exogenous growth factors may be added to direct differentiation of the stem cells, for example, BDNF and NT-3 (col. 2, lines 25-39). They further teach that utilizing these methods they found expression of tyrosine hydroxylase in the resultant neural cells (see col. 56, Table 1).

Thomson and Weiss do not teach that the differentiation medium used to culture the cells contains noggin and follistatin. However, Melton teaches methods for inducing neuronal cell differentiation. Particularly, they teach that stem cells can be induced to differentiate into a committed progenitor cell, or a terminally differentiated neuronal cell by culturing with an agent that antagonizes the biological action of activin, such as follistatin, and a second agent which is a neurotrophic factor that enhances a particular differentiation fate of the cell, such as noggin. See col. 9, lines 8-30 and col. 9-10, bridging ¶ and claims 1, 4 and 13.

Accordingly, in view of the combined teachings of Thomson, Weiss and Melton, it would have been obvious for one of ordinary skill in the art at the time



Art Unit: 1632

the claimed invention was made, to culture stem cells, such as those taught by Thomson to differentiate in a culture medium that contains follistatin and noggin, as taught by Weiss and Melton, to produce neurons that express TH, with a reasonable expectation of success. Furthermore, the claims only require that the resultant population of cells comprise neurons. Thus, one of ordinary skill would have a reasonable expectation of success, given the teachings of Thomson, Weiss and Melton, to produce a TH-expressing neuron from an human ES cell.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Art Unit: 1632

***Conclusion***

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

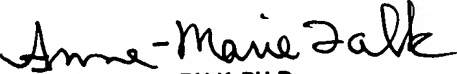
A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

***tnt***

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